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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,880	10/22/2003	Nancy M. Lee	026837-000110US	8369

20350 7590 04/22/2008

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EXAMINER	
SULLIVAN, DANIEL M	
ART UNIT	**PAPER NUMBER**
1636	

MAIL DATE	DELIVERY MODE
04/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,880	LEE ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2007 and 21 February 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-55,57-93,96 and 97* is/are pending in the application.

4a) Of the above claim(s) *1-48,50,65-78,80 and 89-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49, 51-55, 57-64, 79, 81-88, 96 and 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 27 December 2007 has been entered.

This Office Action is a reply to the Papers filed 27 December 2007 and 21 February 2008 in response to the Final Office Action mailed 27 July 2007. Claims 1-48, 50, 65-78, 80, 89-93 have been withdrawn from consideration. Claims 49, 51-64, 79, 81-88 and 96-97 were considered in the 27 July Office Action. Claims 19 and 57 were amended and claim 56 was cancelled in the 27 December Paper. Claims 1-55, 57-93, 96 and 97 are pending and claims 49, 51-55, 57-64, 79, 81-88, 96 and 97 are under consideration.

Response to Amendment and Arguments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 57-59 and 96-97 under 35 U.S.C. 112, first paragraph, as containing new matter is **withdrawn** in view of the amendment of the claims to remove the limitation "independently validated normal control" from the claims.

Claims 49, 51-55, 57-64, 79, 81-88 and 96-97 **stand rejected** under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for the reasons of record and the reasons set forth herein below. The *prima facie* rejection is set forth herein below in revised form to account for the amendments to the claims and to cite additional art relevant to enablement of the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art, the amount of experimentation necessary and the relative skill levels of those in the art. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the Invention: The instant claims are drawn to a method for determination of colorectal cancer and colorectal polyps comprising the selection of a panel of biomarkers comprising at least two polynucleotides from SEQ ID NOs: 1, 2 and 5, obtaining a biological sample from a subject, isolating cellular RNA from the sample, amplifying cDNA from the sample for each biomarker in the panel; quantifying levels of amplified cDNA; and comparing the quantity (presumably of the amplified cDNA) in the sample to a normal control, wherein the difference is indicative of a colorectal cancer and colorectal polyps.

Some claims are further limited to such methods wherein the comparison is used for the management of patient care (claims 57-58) or wherein the comparison is used for the discovery of therapeutic interventions of colorectal cancer and colorectal

polyps (claim 59). Some claims are further drawn to such methods wherein the step of obtaining a sample of colorectal cells in minimally invasive.

The instant claims are also drawn to kits for the determination of colorectal cancer and colorectal polyps comprising at least one reagent used in analysis of polynucleotide expression levels. Some kits further comprise SEQ ID NOs: 45-48, 53-54 and 7-76.

The invention is complex in that it involves measuring a change in the level of RNA by amplification, such that a determination of colorectal cancer and colorectal polyps is made, a subject is identified as a candidate for management of patient care or a therapeutic intervention is discovered.

Breadth of the claims: The claims are extremely broad in that they encompass methods for measuring the expression levels of polynucleotides from any biological sample and comparing such expression levels to any control such that the comparison is determinative of colorectal cancer and colorectal polyps and used in any aspect of the management of patient care in colorectal cancer and colorectal polyps, or such that the comparison is used in the discovery of any therapeutic intervention of colorectal cancer and colorectal polyps. It is further noted that the identification of a subject as a

candidate for the management of colorectal cancer is based on an increase in a single cDNA. The large breadth of the claims exacerbates the complexity of the invention.

Guidance of the specification/The existence of working examples: The specification discloses the use of a mouse multiple intestinal neoplasia (MIN) model to determine expression differences between mouse MIN subjects comprising a chemically induced mutation in the APC gene and normal control littermates for which there was not aberration of the APC gene (page 5, paragraph 18). From these studies candidate genes were selected for study in human subjects; and from these studies with human samples, a disclosed panel of biomarkers was obtained. In one disclosed example, a panel of six biomarkers is used "as the basis for determination of CRC in human subjects" -- although the biomarkers were applied to samples obtained from patients known to have CRC and from individuals validated as normal controls (page 8, paragraph 27). In another example, multiple biopsy samples taken from one exemplary patient diagnosed with CRC showed differences in expression of three biomarkers (see paragraph bridging pages 9 and 10). However, the specification gives no indication of what such a difference in expression means for patient care management or for the discovery of therapeutic interventions. In the last

example, the specification teaches that multiple biopsies (again from a single patient), taken over a 53 cm region of the colon, where able to "distinguish differences in the colon tissue for the patient" whereas the same biopsy samples were rendered normal by conventional histological analysis. The specification teaches that such results demonstrate a minimally invasive swabbing collection method from an area distant from a cancerous lesion is capable of indicating a "non-normal colon condition" (page 10, paragraph 32).

The specification fails to teach how measurements of RNA expression can be used to manage patient care or to discover new therapeutic interventions.

The specification lacks a single example of the use of expression levels of SEQ ID NOs: 1, 2 or 5 in combination to manage patient care or to discover new inventions for CRC or colorectal polyps.

The specification does not teach what differences in expression of SEQ ID NOs: 1, 2 or 5 can be used in order to perform risk assessment, early diagnosis, establishing a prognosis, monitoring patient treatment or detecting relapse. For example, does a decrease in the level of SEQ ID NOs: 1, 2 or 5 indicate that a relapse is likely? How much of a decrease is required for such a conclusion to be reached? Furthermore, the

specification teaches that "mRNA expression levels are not good predictors of protein expression levels, and that mRNA expression levels tell nothing of the post-translational modifications of proteins that are key to their biological activity" (page 7, paragraph 23). Along those same lines, the specification teaches that "in order to understand the expression levels of proteins, and their complete structure, the direct analysis of proteins is required" (ibid). In light of the admitted limitations of using RNA levels, how can such expression levels be used to manage patient care and or discover new interventions for CRC and/or colorectal polyps?

In addition, it is acknowledged in the specification that "there is a distinct difference between research on a specific a gene, its expression, protein product, and regulation, and understanding what genes are critical to include in a panel used to for the analysis of CRC that is useful in the management of patient care for the disease." (paragraph 0017) and the application demonstrates that there is substantial variation in expression levels of individual genes when compared with control sample (paragraph 0027), which necessitates the use of a panel of biomarkers for diagnostic validity. In spite of this, the application seeks to claim a method of using all panels of

biomarkers comprising any two of SEQ ID NO: 1, 2 or 5 to determine colorectal cancer or colorectal polyps and seeks to claim a method wherein an increase in a single cDNA identifies a subject as a candidate for the management of colorectal cancer.

State of the prior art and level of predictability in the art: The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art. Accordingly, what is known in the art provides evidence as to the question of predictability.

The physiological art is recognized as unpredictable. (MPEP 2164.03.) In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws.

In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

In the instant case, the specification teaches that "given the complexity of biological systems, discovery of panels useful in providing value in patient care management for CRC is in the nascent stage" (page 5, paragraph 16). The prior art supports this statement.

In general, the prior art teaches that there are many factors that need to be considered in order to develop a reliable genetic test. The art teaches that before a putative biomarker can be used as a surrogate endpoint it must be validated as such. Wagner (2002) *Dis. Markers* 18:41-46 acknowledges in the Abstract, "Putative biomarkers are typically identified because of a relationship to known or hypothetical steps in a pathophysiologic cascade. Biomarker discovery can also be effected by expression profiling experiment using a variety of array technologies and related methods." However, Wagner cautions, "A rational basis for recommending the use of a putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the left and right columns on page 43) and

"Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44).

Frank *et al.* (2003) *Nature Rev.* 2:566-580 concurs, stating, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568). Feng *et al.* (2004) *Pharmacogenomics* 5:709-719 teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation…A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

The unpredictability of correlating gene expression level to any phenotypic quality is also supported by the teachings of Wu (*J. Pathol.* **195**(1):53-65, 2001.). Wu teaches that gene expression data must be interpreted in the context of other biological knowledge, involving various types of "post genomics"

informatics, including gene networks, gene pathways, and gene ontologies (page 53, left column). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (page 63 – Discussion).

The lack of predictive success of gene expression studies may, in part, be due to the fact that increased mRNA is not always indicative of protein expression levels, as indicated in the specification (cited above). Chen et al (*Molecular and Cellular Proteomics* **1**:304-313, 2002) compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (page 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pages 311-312).

Additional post filing art reveals that most gene association studies are typically wrong. Lucentini (The Scientist, Vol. 18, page 20, 2004) teach that it strikingly common for follow-up studies to find gene-disease associations wrong (e.g. page 2, 1st paragraph). Lucentini teaches that two recent studies found that typically when a finding is first published linking a given gene to a complex disease there is only roughly a one-third chance that the study will reliably confirm the finding (e.g. page 2, 3rd paragraph). Lucentini teaches that bigger sample sizes and more family-based studies, along with revising statistical method, should be included in the gene association studies (e.g. page 3, 2nd paragraph).

In post-filing art, Barrier et al (*Oncogene* 24:6155-6164, 2005; IDS Ref) teach the attempted construction of a prognosis predictor model for stage II and stage III colon cancer based on gene expression measurements that involve a number of genes, but which do not involve the claimed panel of biomarkers (see entire document, especially pages 6156-6158). However, Barrier concedes that the results of the study only "suggest the possibility to build an accurate prognosis predictor using gene expression profiles" and that the study "has to be confirmed by larger other studies" (see page 6162, first full paragraph). In other post-filing art, Hao et al (*Clinical Cancer Research*

11:1400-1407, 2005; IDS Ref.) teach that gene expression of the claimed sequences is altered in macroscopically normal colonic mucosa from individuals with a family history of sporadic colon cancer, but that prospective studies will be needed "to determine whether or not altered gene expression is associated with the subsequent development of adenomatous polyps and/or colonic carcinomas" (see entire document, especially the Abstract).

Thus, the state of the art is underdeveloped with respect to the use of nucleic acids to diagnose and manage disorders in general; the state of the art is also underdeveloped with respect to the use of nucleic acids for the management of patient care and discovery of therapeutic interventions for CRC and colorectal polyps in particular.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, one of ordinary skill would not be able to make and use the invention now claimed and as asserted in the application without undue experimentation. The specification discloses a single panel of genes exhibiting altered expression in a mouse model comprising a chemically induced mutation in the APC gene and normal control littermates for which there was not aberration of the APC gene and analysis

of a panel of six biomarkers applied to samples obtained from patients known to have CRC and from normal controls. The application also discloses differences in expression of three biomarkers in biopsy samples taken from one exemplary patient diagnosed with CRC.

Based on this disclosure, the application seeks to claim a method comprising measuring expression of any panel of biomarkers comprising any two polynucleotides selected from SEQ ID NO: 1, 2 and 5 expressed in any biological sample and comparing such expression levels to any control, wherein the comparison is determinative of colorectal cancer and colorectal polyps and used in any aspect of the management of patient care in colorectal cancer and colorectal polyps, or such that the comparison is used in the discovery of any therapeutic intervention of colorectal cancer and colorectal polyps.

However, the art cited above clearly evidences that establishing expression of any single gene in any given cell system as a valid biomarker for any given condition is highly unpredictable and requires careful validation. This is acknowledged in the instant specification, which teaches that, "there is a distinct difference between research on a specific a gene, its expression, protein product, and regulation, and understanding what genes are critical to include in a panel used

to for the analysis of CRC that is useful in the management of patient care for the disease." (*Id.*) and that "given the complexity of biological systems, discovery of panels useful in providing value in patient care management for CRC is in the nascent stage" (*Id.*). In addition, as discussed above, the application teaches that there is substantial variation in expression levels of individual genes when compared with control sample (paragraph 0027), which necessitates the use of a panel of biomarkers for diagnostic validity.

Given the nascent and unpredictable state of the relevant art, one of ordinary skill would be required to empirically determine which panels of biomarkers and which biological samples within the expansive scope of the instant claims could be used to determine colorectal cancer and colorectal polyps in any given subject. Furthermore, one would be required to establish how RNA expression from genes of any given panel of biomarkers in any given biological sample correlates with any aspect of the management of patient care in colorectal cancer and colorectal polyps or with the therapeutic efficacy of an intervention. In view of the complex nature of the invention and the underdeveloped state of the art at the time of filing, which is acknowledged in Applicant's own specification, and the

broad scope of the claims, there would be a large and prohibitive amount of experimentation required to make and use the claimed invention. Even for claims specifically reciting SEQ ID NOs: 1, 2, 5, 15 and 16 with particular samples from diseased tissue, one would have to establish that the differences in expression were statistically significant reliably correlated with the presence of colorectal cancer and polyps, risk assessment, prognosis and therapeutic effect. This would include analysis of the different levels of expression in a large number of individuals first to establish what level of gene expression is considered "elevated" or "decreased" relative to a "normal" level of expression.

In view of the foregoing, the skilled artisan would not be able to make and use the invention presently claimed without first engaging in undue experimentation. Therefore, the claims are properly rejected under 35 USC § 112, first paragraph, as lacking an enabling disclosure.

Response to Arguments and the Declaration of Dr. Nancy M. Lee under 37 CFR §1.132.

Declaration

The opinions expressed beginning in the paragraph numbered 6 on page 1 of the declaration through the first paragraph on the third page of the declaration pertain to the written description rejection. As the rejection has been withdrawn herein, those remarks will not be addressed herein.

Beginning in the second paragraph number 6 (page 3), the declaration describes experiments purported to establish a correlation between changes in expression of the SEQ ID NO: 1, 2 and 5 sequences and the presence of colorectal cancer and colorectal polyps. The data presented were obtained by rectal swab from normal appearing mucosa about 5-10 cm before the rectum of the subjects. RNA was isolated from the swab samples and RT-PCR'ed using the primers identified in the specification.

Validated controls were identified by determining the subject's family history and self history of cancer and the subject's own upper GI diseases and disorders. In addition, morphological identification of polyps and cancerous lesions identified during colonoscopy were also used to categorize subjects.

Marker expression was quantified (presumably by real time quantitative PCR although the declaration does not make this clear) and the data are analyzed by the ΔΔCT method. The

results, presented in Table 1, are characterized by Applicant as follows:

> Looking at Table I, for example, IL-8 in the control group has a ΔΔCT of 0.0050 and the cancer (PBS) group has a ΔΔCT of -3.191, an increase in IL-8 expression in the cancer group compared to control. As demonstrated by the data above, measuring at least two markers selected from IL-8, COX2 and SAA-1 provides information regarding the subject's disposition and development of polyps or cancer. (1) where an increase in IL-8 and COX2 is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (2) where an increase in IL-8 and SAAl is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (3) where an increase in COX-2 and SAAl is present in the subject compared to a control, the subject has or is at risk of having colorectal cancer or polyps; (4) where an increase in IL-8, COX2 and SAA1 is present in the subject compared to control the subject has or is at risk of having colorectal cancer or polyps; and (5) where an increase and then a decrease in SAAI is observed and an increase of IL-8 and/or COX2 is observed the subject had polyps and has transitioned to colorectal cancer. As indicated above, SAAl is a biphasic marker meaning that it changes during disease progression; however, SAA1 is elevated compared to control both at the polyp and cancer stages.

Declarant concludes that the data demonstrate that the measurement of any two biomarkers selected from IL-8, COX2 and SAA1 provide evidence of colorectal cancer or polyps in a subject when compared to controls as originally indicated,

contemplated and claimed by the present application and currently claimed.

The Declaration under 37 CFR 1.132 is insufficient to overcome the rejection of claims 49, 51-55, 57-64, 79, 81-88 and 96-97 based upon insufficiency the disclosure under 35 USC § 112, first paragraph, as set forth herein above, in view of the evidence as a whole.

First, the showings of the declaration do not evidence enablement for the full scope of the claimed invention. As an initial matter, it is noted that the claims do not require that expression of any of the biomarkers comprising SEQ ID NO: 1, 2 or 5 actually be measured in the method. Claim 49 requires that a panel comprising SEQ ID NO: 1, 2 and 5 is selected. However, the steps of amplifying and quantifying levels of cDNA make no reference to SEQ ID NO: 1, 2 or 5 and might, in fact, be wholly independent of the selected panel of biomarkers. Therefore, the claims embrace determining colorectal cancer and colorectal polyps based on quantities of cDNAs that may or may not include SEQ ID NO: 1, 2 or 5. Clearly the declaration does not evidence enablement for such scope.

Similarly, even if you were to assume that claim 49 required that expression of cDNAs comprising SEQ ID NO: 1, 2 or 5 be measured, which it does not, claim 57 would still embrace

the method wherein the diagnosis is based on expression that is independent of any of the sequences SEQ ID NO: 1, 2 or 5. That is because the panel of biomarkers of claim 49 "comprises" the recited sequences (i.e., comprises the recited sequences and infinite undefined sequences) and claim 57 does not specify that the cDNA that identifies the subject as a candidate for management of colorectal cancer and colorectal polyps is any of the cDNAs defined by the SEQ ID NOs: 1, 2 or 5. The evidence presented clearly does not demonstrate that applicant had enabled a method of identifying a subject as a candidate for the management of colorectal cancer and colorectal polyps based on an increase in any single cDNA that might happen to be expressed in a cell.

Likewise, even if you were to assume that claim 49 required that expression of cDNAs comprising SEQ ID NO: 1, 2 or 5 be measured, the process presented in the declaration involves obtaining a biological sample of intestinal mucosa while the claims, in their broadest aspect, cover obtaining any biological sample (e.g., blood sample). Thus, even if one accepts that the declaration indicates enablement for the method wherein the sample obtained is intestinal mucosa, *arguendo*, the claimed scope is much broader than what is enabled.

Still further, again assuming that the claims required measurement expressed SEQ ID NO: 1, 2 or 5, the Declaration does not evidence enablement for "determination of colorectal cancer and colorectal polyps". According to Declarant's own assessment of the data, an increase in any of the defined sequences or combination of the defined sequences does not distinguish a subject having colorectal cancer and colorectal polyps from a subject at risk of having colorectal cancer or polyps. (See points 1-4 in the first full paragraph on page 8 of the declaration.) In contrast, the Declaration states that the diagnosis of cancer and polyps (i.e., determination of colorectal cancer and colorectal polyps as required by the claims) is based on "an increase and then a decrease in SAA1 and an increase of IL-8 and/or COX2". Therefore, the Declaration evidences that determining colorectal cancer and polyps as recited in the instant claims is based on a biphasic response of SAA1. However, as this biphasic response is not disclosed in the instant application, the Declaration evidences that practicing the method as claimed requires information that was not disclosed in the application as of its filing date. Therefore, the Declaration clearly evidences that the skilled artisan would not have been enabled by the specification to determine colorectal cancer and colorectal polyps at the time of filing.

Finally, the Declaration provides no evidence at all that biomarkers comprising SEQ ID NO: 1, 2 or 5 can be used to assess the efficacy of a therapeutic intervention or how to obtain outcomes such as establishing prognosis as recited in claim 58.

Thus, in view of the evidence considered as a whole, it is concluded that the Declaration fails to establish that one of skill in the art would have been enabled to make and use the invention presently claimed without undue experimentation.

Applicant Arguments

In the remarks, Applicant first cites a passage from the previous Office Action (at page 11) wherein the examiner points out that much of the evidence cited by Applicant to support enablement for the claimed invention does not include data for the specific "biomarkers" recited in the instant claims. Applicant points out that the claimed invention, as filed, comprised measuring a plurality of markers (e.g., SEQ ID NOs:1-22) IL-8, COX2 and SAA1 (SEQ ID NO: 1, 2 and 5, respectively). Applicant submits that SEQ ID NOS; 1, 2 and 5 were included in the claimed invention and that these elements are currently pending in the claims before the Examiner.

In response, it is noted that the Examiner's point in the cited passage is not that the application does not assert that

the recited biomarkers can be used as claimed. The Examiner's point is that the evidence provided does not establish that the method could be practiced as claimed given the highly unpredictable state of the art, which, as pointed out on page 12 of the previous Office Action, is evidenced by Applicant's own statements in the specification.

Next, Applicant cites the attached 1.132 Declaration by Dr. Nancy Lee and submits that the Declaration provides evidence, in addition to that in the specification, that measurement of IL-8, COX2 and SAA-1 ("at least two from SEQ ID NOS 1-5") are changed (e.g., increased) relative to controls. Applicant further submits that the data presented in the specification, as filed, and in the attached Declaration demonstrate the invention as it relates to the claimed biomarkers and those subject to restriction in the present application. Applicant concludes that the claimed invention as filed is fully enabled by the specification because the specification teaches that measurement of biomarkers selected from SEQ ID NOS 1- 22, including SEQ ID NOS: 1, 2, 5, 15 and 16 (IL-8, COX2, SAA-1, PPAR–α and PPAR-γ) can be used to identify a subject having or at risk of having colorectal cancer or polyps.

These arguments have been fully considered but are not persuasive in view of the record as a whole. As described above,

the evidence presented in the Declaration does not show enablement for the full scope of the claimed invention and actually demonstrates that determination of colorectal cancer and colorectal polyps requires knowledge of the biphasic nature of SAA-1 expression, which is not disclosed in the instant application. It is again noted that none of the instant claims actually requires that the determinations recited in the claims is based on expression of any of the markers identified as SEQ ID NO: 1, 2 or 5. Instead the claims merely require that a panel of biomarkers comprising at least two polynucleotides form SEQ ID NO: 1, 2 and 5 is selected. There is no requirement that a change in the expression of the recited sequences is used to determine the outcome recited in the claims. In fact, the claims do not even recite that the quantifying step uses the panel of biomarkers selected in the earlier step. Therefore, the claims do not require even that expression of the markers identified by SEQ ID NO: 1, 2 or 5 is determined. Clearly, given the highly unpredictable state of the art, the claims are not enabled for such expansive scope. In addition, no guidance is provided with regard to how to obtain outcomes such as “establishing prognosis” and "discovery of therapeutic intervention” as recited in the claims.

Thus, in view of the expansive scope of the claims, the unpredictable state of the art, and the failure of the application to provide information critical to practicing the invention as claimed one of skill in the art would not have been able to make and used the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 79, 81-83, 86, 87 and 88 are rejected under 35 U.S.C. 102(b) as being anticipated by TaqMan® EZ RT-PCR kit Protocol, Applied Biosystems, Printed in the USA, 4/2002 (hereinafter, the TaqMan® protocol).

The claims are directed to a kit for the determination of colorectal cancer and colorectal polyps comprising at least one reagent that is used in the analysis of polynucleotide expression levels for a panel of biomarkers, wherein the panel comprises at least two polynucleotides listed in SEQ ID NO: 1, 2

and 5 and instructions for using the kit for analyzing expression levels.

The claims are construed as follows: The intended uses recited in the claims (i.e., "for the determination of colorectal cancer" and "used for the analysis of polynucleotide expression levels for a panel of biomarkers") are viewed as limiting the kit of the claim only insofar as the reagent of the kit must be capable of use in a method for the determination of colorectal cancer. (See, e.g., MPEP 2111.02.)

The TaqMan® protocol describes a kit comprising numerous reagents that could be used in a method as recited in the claims. (See, e.g., page 1-6.) With regard to the limitation that the panel comprises certain specific biomarkers, it is noted that the claims do not require that the kit itself comprise the recited biomarkers and, because the reagents provided with the TaqMan® kit are not sequence specific, they could be used in the analysis of polynucleotide expression for any panel of biomarkers, including those recited in the claims. Thus, the TaqMan® protocol anticipates the kit of the instant claims 79, 81-83 and 86. Furthermore, the kit includes a fluorogenic probe (i.e., a chromophore; GAPDH probe on page 1-6) according to the limitations of claim 87 and tubes (i.e., labware) according to the limitations of claim 88.

The kit described in the TaqMan® protocol comprises all of the elements of the invention presently claimed. Therefore, the claims are anticipated by the art.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M. Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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